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Estimating the public health importance of the CYD-tetravalent dengue vaccine: Vaccine preventable disease incidence and numbers needed to vaccinate

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ABSTRACT

Background: To evaluate the potential public health impact of the live attenuated tetravalent Sanofi Pasteur dengue vaccine (CYD-TDV) we analyzed data from the reported clinical trials to calculate vaccine preventable disease incidence (VPDI) and number needed to vaccinate (NNV) based on the licensure indication for persons age 9 years and above.
Methods: VPDI is defined as incidence in an unvaccinated population X vaccine efficacy (VE), and thus incorporates both VE and the underlying burden of disease. NNV was calculated as 100,000 divided by VPDI divided by 2-year length of study. We compared these values to data for three newer vaccines that are currently integrated into some national immunization programs in Asia and Latin America, namely pneumococcal conjugate, *Haemophilus influenzae* type b, and rotavirus vaccines.
Results: In the Asian-Pacific trial, in the first 25 months after the first dose of the dengue vaccine, CYD-TDV prevented annually 2639 cases of virologically confirmed dengue for every 100,000 persons vaccinated, for an NNV of 18. In the Latin American trial, given the overall lower annual dengue incidence compared to Asia, VPDI was 1707, and NNV 28. For the Asian-Pacific and Latin American studies, the VPDIs for hospitalized virologically confirmed disease at the trials' end were 638 and 239 per 100,000 population per year, respectively, with NNVs of 75 and 201. VPDI for confirmed dengue hospitalization was higher than that for Hib vaccine against Hib meningitis or all cause severe pneumonia while lower than that for rotavirus vaccine against severe rotavirus gastroenteritis.
Conclusions: Our analysis found that the CYD-TDV dengue vaccine had favorable VPDI and NNV, also when compared to existing vaccines used in Latin America and Asia. VPDI and NNV varied by serotype distribution, extent of prior dengue exposure (baseline seroprevalence) and country. These findings will help policy-makers decide where and how to introduce this vaccine post-licensure.

1. Introduction

Dengue is an arboviral disease that poses a significant public health burden in most countries in the tropics and subtropics. With some 100 million cases estimated to occur annually, many of which lead to hospitalizations, dengue outbreaks can overwhelm already fragile health care systems [1]. The often unpredictable nature of dengue outbreaks further aggravates the public health impact. The increasing incidence and geographic expansion of dengue transmission in the past two decades, accompanied by the increasing socioeconomic burden compounded by costly yet still ineffective vector control strategies, underpin the urgent need for a dengue vaccine [2].

The live attenuated recombinant tetravalent Sanofi Pasteur dengue vaccine CYD-TDV was assessed during a 25-month efficacy surveillance phase (Phase 3 trial). Conducted in ten endemic countries in Asia and Latin America, two multi-center efficacy trials involved more than 31,000 subjects with an age range from 2 to 16 years [3,4]. The overall efficacy for all age groups in both trials was 54% for virologically confirmed dengue of any severity or

Abbreviations: Hib, *Haemophilus influenzae* type b; NNV, number needed to vaccinate; RCT, randomized clinical trial; VE, vaccine efficacy; VPDI, vaccine preventable disease incidence.

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serotype [5]. The efficacy against virologically confirmed dengue of any severity and serotype, hospitalizations, and severe disease was consistently higher in those aged 9–16 years than younger subjects [5]. Because of the lower efficacy and the transient reversed risk:benefit observed in the third year in younger children [5] the age group anticipated to benefit most from this vaccine, and the age group for which the manufacturer is seeking licensure, is individuals from the age of 9 years and above [6]. In this age group, the overall efficacy in the first 25 months (13 months after the third dose) against virologically confirmed dengue was 65%, against hospitalization 81% and against severe disease 93% [5]. Follow-up is still ongoing to assess long-term efficacy and safety. Meanwhile, the vaccine has been licensed in at least 4 countries for the age range of 9–45 years.

Efficacy results obtained from randomized controlled trials (RCTs) are important for licensure. In an RCT, efficacy provides a measure of proportionate reduction at individual level. However, evidence-informed introduction of vaccines into national programs, once a dengue vaccine is indeed licensed, cannot only be driven by efficacy because efficacy indicates whether a vaccine works against a specific outcome rather than providing information on the vaccine's public health impact. In addition to the prevention of infection at individual level, the ultimate goal of vaccination is to decrease the public health burden of disease at the population level. Hence, an additional measure to efficacy that more directly establishes a vaccine's public health importance is the vaccine preventable disease incidence (VPDI) [7]. VPDI is the incidence of given disease syndrome preventable by vaccine in a given context [7]. Furthermore, the number needed to vaccine (NNV) is often used as a metric of the value of vaccination programs, and can also be used for cost effectiveness studies. NNV is a measure to quantify the number of people, or the number of vaccine doses, needed to prevent one event due to disease and allow the calculation [8].

To evaluate the potential public health impact of the CYD-TDV dengue vaccine beyond the efficacy data already published, we analyzed data from the previously reported clinical trials [3–5] to calculate VPDI and NNV based on the target indication of ages 9 years and above. To provide context to these findings, for Latin America we compare these values to data for three vaccines with clinical trial data from Latin America and that are currently integrated into most national immunization programs in the region, namely pneumococcal conjugate [9], *Haemophilus influenzae* type b [10], and rotavirus vaccines [11].

2. Methods

Measurement of VPDI is defined as: incidence in an unvaccinated population X vaccine efficacy (VE), and thus incorporates both VE and the underlying burden of disease [12]. This is mathematically equivalent to the incidence in the control group minus the incidence in the intervention group. In principle VPDI is best calculated from community randomized trials as this allows incorporation of the vaccine's ability to prevent disease through both direct and indirect mechanisms. Additionally, it is best calculated for clinically rather than etiologically defined endpoints as this adjusts for the inevitable failure to confirm all prevented outcomes. However, currently published data [3–5] are limited to the individually randomized trials that report VE against etiologically defined outcomes, which will provide a lower bound of true VPDI.

While incidence densities for all virologically confirmed dengue were presented in the separate regional reports [3,4], these reports did not present data that would allow incidence calculations for severe or hospitalized dengue and the Asian manuscript did not present data separately for the 9–16 year old age group. Consequently, we used the pooled analysis [5] for the current study, based on intention-to-treat analysis, as this presented data on all and hospitalized virologically confirmed dengue stratified by age group. For children age 9–16 years, data for all dengue were obtained from Figure 2 and for hospitalized dengue from Figure 3 [5]. Because summary years of follow-up were not reported,

Table 1
Calculation of dengue vaccine preventable disease incidence (VPDI) and number needed to vaccinate (NNV) (with confidence intervals) based on two-year follow-up data for virologically confirmed dengue cases, calculated from data abstracted from Figures 2 and 3 of Ref. [5].

Outcome	Region	Intervention cases	Control cases	Intervention incidence[a]	Control incidence[a]	Vaccine efficacy	VPDI* (95% CI)[a]	NNV (95% CI)
Hospitalized dengue								
All hospitalized	Both regions	27	70	75	391	81%	316 (226, 422)	152 (114, 213)
	Asian-Pacific	10	27	151	815	82%	638 (365, 1008)	75 (48, 132)
	Latin America	17	43	61	310	80%	239 (154, 346)	201 (139, 313)
Severe hospitalized	Both regions	3	22	8	123	93%	114 (72, 178)	419 (270, 667)
	Asian-Pacific	2	11	29	319	91%	290 (130, 528)	166 (91, 370)
	Latin America	1	11	3	76	96%	73 (34, 134)	661 (357, 1429)
All dengue cases								
All serotypes	Both regions	367	521	1022	2909	66%	1887 (1632, 2160)	25 (22, 29)
	Asian-Pacific	90	136	1357	4106	68%	2639 (1968, 3360)	18 (14, 24)
	Latin America	277	385	995	2774	65%	1707 (1440, 2016)	28 (24, 33)
Serotype 1	Asian-Pacific	36	52	543	1570	66%	986 (576, 1488)	49 (32, 83)
	Latin America	99	109	356	785	55%	412 (264, 576)	116 (83, 182)
Serotype 2	Asian-Pacific	33	26	498	785	37%	276 (0, 672)	174 (71, undefined)
	Latin America	84	84	302	605	50%	291 (158, 437)	165 (110, 303)
Serotype 3	Asian-Pacific	11	18	166	543	70%	363 (134, 672)	132 (71, 357)
	Latin America	55	106	198	764	74%	543 (403, 720)	88 (67, 119)
Serotype 4	Asian-Pacific	10	41	151	1238	88%	1044 (720, 1488)	46 (32, 67)
	Latin America	32	83	115	598	81%	464 (346, 624)	104 (77, 139)
Baseline seropos.[b]	Asian-Pacific	7	17	690	3251	79%	2561 (1162, 4416)	19 (11, 41)
	Latin America	8	23	358	2156	84%	1798 (1008, 2832)	27 (17, 48)
Baseline seroneg.[b]	Asian-Pacific	7	8	2605	6508	62%	3904 (−149, 9360)	12 (5, undefined)
	Latin America	9	9	1674	2899	43%	1225 (−768, 3768)	39 (13, undefined)

[a] Annual incidence per 100,000 persons.
[b] Baseline seropositivity was determined for only a subset of enrolled subjects; consequently, the denominator for these outcomes is different than for all other outcomes. Denominators for the Asian-Pacific region were 3316 and 1656 for vaccinated and control subjects, respectively, for all enrolled subjects and for Latin America 13,914 and 6940. For baseline seropositive, denominators for the Asian-Pacific region were 487 and 251 for vaccinated and control subjects and for Latine America 1073 and 512. For baseline seronegative, denominators for the Asian-Pacific region were 129 and 59 for vaccinated and control subjects and for Latin America 258 and 149.

Table 2
Calculation of dengue vaccine preventable disease incidence (VPDI) and number needed to vaccinate (NNV) per country, in Latin America[a] based on 25 months follow-up data for virologically confirmed dengue cases.

Country	Control incidence density	Vaccine efficacy (VE)	VPDI[b]	NNV
Brazil	3.7	77.5%	2.9	17
Colombia	2.7	67.5%	1.8	27
Honduras	4.0	71.1%	2.8	18
Mexico	2.5	31.3%	0.8	64
Puerto Rico	1.6	57.6%	0.9	54

[a] The only published data stratified by country for the Asian-Pacific region are in Appendix Table 1 [3] and these include all age groups down to age 2 years. Consequently, we do not present country-stratified data for this region.
[b] VPDI for Latin America was calculated from Table S1 [4] as control group incidence density multipled by vaccine efficacy. Raw data were not presented, so confidence limits were not calculated.

we estimated incidence as cases divided by number of subjects enrolled divided by length of the study, in this case 25 months or 2.1 years, times 100,000 to provide cases prevented per 100,000 persons per year. Unlike VPDI, NNV is not a rate but instead the overall number of cases prevented for a given number of persons vaccinated, and thus incorporates the length of the trial. NNV was calculated as (100,000 divided by VPDI divided by 2.1-year length of study).

To calculate the 95% confidence intervals for VPDI in Table 1, we used Vassarstats (website: http://vassarstats.net/prop2_ind.html, last accessed February 28, 2016) as in this case VPDI was calculated as the difference between annual incidences. For Table 2, we used OpenEpi (website: http://www.openepi.com/PersonTime2/PersonTime2.htm, last accessed February 28, 2016) to calculate the VPDI 95% confidence intervals since in this case incidence densities were available.

Decision-makers do not judge a vaccine's importance in a vacuum but rather against other options for public health interventions. To provide context, for Latin America we compared the calculation of VPDI and NNV for dengue vaccine to that for pneumococcal conjugate [9], Hib [10], and rotavirus [11] vaccines. For Asia, we used comparison data for Hib [13] and rotavirus [14] vaccines. These vaccines were selected for two reasons: (1) clinical trials existed specifically from Latin America or Asia that allowed calculation of VPDI and in all cases but the Asian Hib vaccine study for NNV; (2) some or most countries in the respective region have included these vaccines in their national immunization programs and thus have already concluded that they represent efficient use of resources. A specific subtlety was that some studies used person-years of observation and others used persons vaccinated to calculate incidences in study groups, and this is noted in the data we present. Calculation of NNV in all cases was done only if the number of persons vaccinated by intervention and control populations was available.

3. Results

For the primary endpoint of all virologically confirmed dengue cases in subjects aged 9 years and above, based on VE data reported at the 2.1 year follow-up, the Asian Pacific study reported control and intervention group annual incidences of 3942 and 1303 per 100,000 vaccinated subjects, respectively, which translates into an annual VPDI of 2639 per 100,000 (Table 1). Phrased differently, the CYD-TDV dengue vaccine prevented 2639 cases of virologically confirmed dengue yearly for every 100,000 persons vaccinated, for an NNV over the 2.1 year study period of 18. Similar results for control and intervention group incidences and VPDI in the Latin American study were 2663, 956, and 1707 per 100,000 population; the NNV was 28. For the Asian-Pacific and Latin American regions, the annual VPDIs for hospitalized virologically confirmed disease at the end of two years were 638 and 239 per 100,000 population, respectively, with NNVs of 75 and 201, with lower VPDIs and higher NNVs for severe hospitalized dengue.

Serotype 4 had the most favorable VPDI and NNV, followed by serotype 1 (Table 1). Among the subgroup with baseline seroprevalence determined, VE was lower in both Asia and Latin America for those who were seronegative. Despite this, in Asia VPDI was higher and NNV lower for persons seronegative at baseline while the opposite was true in Latin America; this result is tempered however by the wide confidence intervals in the seronegative group. Variations in VPDI and NNV also occurred by individual country in Latin America (Table 2). Mexico for example had a lower VPDI and higher NNV than Brazil, due to a lower baseline control group incidence combined with a lower vaccine efficacy; the latter in turn may relate to a lower baseline dengue seropositivity status in Mexico and different circulating serotypes.

Compared to studies of pneumococcal, Hib, and rotavirus vaccines in Latin America, dengue vaccine efficacy was similar

Table 3
Comparison of vaccine preventable disease incidence (VPDI) and number needed to vaccinate (NNV) for dengue vaccine compared to other vaccines evaluated and introduced into national immunization programs in Latin America. VPDI reported as cases per 100,000 vaccinated persons per year except where otherwise noted.

Etiology	Outcome	Vaccine efficacy (95% CI)	VPDI	NNV
Dengue [5][a]	All virologically confirmed clinical cases	65% (59, 70)	1707	28
	All virologically confirmed hospitalized cases	80% (65, 89)	239	201
	All virologically confirmed severe hospitalized cases	96% (69, 100)	73	661
Rotavirus [11][b]	Confirmed rotavirus hospitalization	85% (70, 94)	870	200
	All cause gastroenteritis hospitalization	42% (29, 53)	1790	97
	All cause severe gastroenteritis hospitalization	40% (28, 50)	2080	84
Pneumococcus [9][c]	Vaccine serotype invasive pneumococcal disease	100% (77, 100)	152	1779
	Consolidated community acquired pneumonia (CAP)	22% (8, 34)	600	448
	CAP with radiographic confirmation of consolidation or pleural effusion	10% (2, 18)	800	306
	Clinically suspected CAP	9% (4, 14)	1800	135
Haemophilus influenzae type b (Hib) [10][d]	All pneumonia hospitalizations with consolidation, effusion, bronchial breath sounds, or elevated erythrocyte sedimentation rate	26% (7, 44)	250	Not available

[a] Data calculated for persons 9 to 16 years of age and 2 year follow-up period.
[b] Data from 10 Latin American countries plus Finland, for infants followed from infant immunization to age 1 year.
[c] Data from three Latin American countries, for children followed from infant immunization to average of almost 3 years. VPDI reported as cases per 100,000 person-years of observation (PYO).
[d] Data from Chile, for children followed infant immunization to age 2 years. VPDI reported as PYO.

Table 4
Comparison of vaccine preventable disease incidence (VPDI) and number needed to vaccinate (NNV) for dengue vaccine compared to other vaccines evaluated and introduced into national immunization programs in the Asian-Pacific region. VPDI reported as cases per 100,000 vaccinated persons per year except where otherwise noted.

Etiology	Outcome	Vaccine efficacy (95% CI)	VPDI	NNV
Dengue [5] [a]	All virologically confirmed clinical cases	68% (58, 76)	2639	18
	All virologically confirmed hospitalized cases	82% (61, 92)	638	75
	All virologically confirmed severe hospitalized cases	91% (58, 99)	290	166
Rotavirus [14] [b]	Severe rotavirus gastroenteritis (Vesikari score 11+)	48% (22, 66)	3000	29
	All cause severe gastroenteritis	27% (2, 46)	3000	38
Haemophilus influenzae type b (Hib) [13] [c]	Hib meningitis hospitalization	86%	16	Not available
	All cause meningitis hospitalization	22%	158	Not available
	All cause severe pneumonia	5%	264	Not available
	All cause clinical pneumonia	4%	1561	Not available

[a] Data calculated for persons 9–16 years of age and 2 year follow-up period.
[b] Data from Bangladesh and Vietnam, for children followed from infant immunization to age 2 years, VPDI reported as cases per 100,000 person-years of observation (PYO).
[c] Data from Indonesia for children followed infant immunization to age 2 years. VPDI reported as PYO.

against etiologically confirmed disease (Table 3). Unlike the dengue vaccine trial, trials of the other three vaccines also presented data on VE against clinical syndromes including pneumonia outcomes for pneumococcus and Hib and all cause gastroenteritis for rotavirus. As expected, VE was lower against these clinical syndromes reflecting that other etiologies were involved. However, VPDI was relatively high indicating that even with relatively low efficacy, vaccines can have high impact when background disease rates are high. VPDI for confirmed dengue hospitalization was similar to that for pneumococcal conjugate vaccine against vaccine serotype invasive pneumococcal disease and Hib vaccine against all cause pneumonia but was lower than that for rotavirus vaccine against all cause severe gastroenteritis and pneumococcal conjugate vaccine against all cause pneumonia.

Compared to studies of Hib and rotavirus vaccines in Asia, dengue vaccine efficacy again was similar against etiologically confirmed disease (Table 4). VPDI for confirmed dengue hospitalization was higher than that for Hib vaccine against Hib meningitis or all cause severe pneumonia while lower than that for rotavirus vaccine against severe rotavirus gastroenteritis.

4. Discussion

Policymakers consistently state that national disease burden is the most important factor in setting priorities for vaccines to be introduced into public sector immunization programs [15]. Despite this, results from vaccine clinical trials focus on the regulatory concerns of vaccine efficacy and safety among individual vaccinated subjects and rarely present data in a way that allows assessment of the expected burden reduction, and thus public health importance, that vaccines can achieve. In the absence of this information, policymakers and public health advisory groups in affected countries may have difficulty making rational recommendations and decisions on whether and how to introduce new vaccines.

Here we present an analysis of data from dengue vaccine clinical trials to illustrate the utility of VPDI, a measure recently described in detail [7,12]. This outcome provides a measure of a vaccine's public health impact by defining how many outcomes can be prevented over a certain time period by delivering a defined quantity of vaccine. The related measure of NNV not only provides a measure of immediate relevance to policy-makers, but also incorporates the concept of cases potentially prevented over multiple years following primary immunization. Both measures will vary with underlying disease epidemiology, such as baseline burden, seasonality, age distribution and where relevant serotype or serogroup distribution. Less well appreciated is that VE also is not an invariant quality and can vary by measured outcome (e.g., lower dengue VE against non-severe than hospitalized disease) and geography (e.g., lower rotavirus VE in Malawi than South Africa [16]).

Our analysis found that the CYD-TDV dengue vaccine had favorable VPDI and NNV when compared to existing vaccines used in Latin America and Asia. For example, in Asia, the CYD-TDV dengue vaccine had a VPDI for severe hospitalized disease approximately equal to the VPDI for severe Hib pneumonia. In Latin America, while severe disease VPDI was relatively low, the VPDI for all hospitalized dengue was approximately equal to the sum of invasive Hib disease and severe pneumonia.

Moreover, dengue vaccine had a high VPDI against less severe disease, which may have substantial implications for health service utilization. Despite the lower VE against serotype 2, the relatively higher incidence of this serotype led to a VPDI within the range of other serotypes with the notable exceptions of serotypes 1 and 4 in the Asian-Pacific region. Lastly, we found variation by baseline seropositivity (among the subgroup that had seroprevalence determined) but not co-linear with VE. For example, in Asia the VPDI was higher and the NNV lower among those who were seronegative at baseline despite a substantially lower VE among this group.

This occurred despite available data being limited to etiologically confirmed disease for dengue while comparisons were made to VDPIs based on syndromic disease. VPDI for dengue was calculated for etiologically confirmed disease while comparison conditions were calculated in part against syndromic disease. VPDI calculated for etiologically confirmed disease likely will be lower than that for syndromic disease because diagnostic tests have imperfect sensitivity, not all persons with suspected dengue are tested, and system errors (e.g., delays between specimen collection and processing) can lead to false negatives. In Finland, for example, rotavirus vaccine prevented over twice as many cases of all cause as rotavirus-confirmed inpatient acute gastroenteritis [17]. Additionally, the individually randomized nature of the dengue trials prevented inclusion of indirect effects. Consequently, the values presented here should be considered a lower bound on the dengue vaccine's ability to reduce burden.

VPDI is an important measure but other issues affect a vaccine's public health importance [18]. For example, dengue vaccine in principle can prevent disease across all age groups while the benefits of rotavirus and largely Hib vaccine are limited to early childhood. Furthermore, a dengue vaccine can prevent the potentially large effects of dengue outbreaks on health, health systems, and the economy [19]. On the other hand, dengue rarely causes significant long-term sequelae and has a relatively low mortality rate [2], similar to rotavirus but distinct from the devastating sequelae and high mortality often caused by invasive pneumococcal and Hib disease.

Our study was not set out to address safety issues and is limited to the first 2 years of the trial. During the third year of the CYD-TDV trial, a higher number of hospitalizations were observed in the vaccinated group compared to the unvaccinated group for those individuals of 2 to 5 years of age. The reversed risk:benefit ratio is

of concern and further long-term follow-up of the phase 3 study participants is ongoing. No such reversed risk:benefit ratio was observed in subjects aged 9–16 years – the age group for which licensure has been sought [20]. Because of the ongoing concern about potential antibody-dependent enhancement at the time of waning efficacy, the World Health Organization recommends that surveillance for possible immune enhanced disease should be continued for 5 years after vaccination [21]. Waning efficacy after two years may occur [22]. However, such waning will not affect the VPDI and NNV estimates presented here as these estimates derived directly from the clinical trial results during the two-year reporting period. Waning immunity may diminish VPDI and NNV beyond the two-year period. Studies are currently being introduced by Sanofi Pasteur to evaluate the need and timing of vaccine boosters.

Our data on VPDI and NNV can aid in cost effectiveness studies once the price of the vaccine is known. Other issues that will need to be addressed include issues such as immune duration, variable distribution of disease burden within countries, and programmatic issues such as vaccine schedule requirements. Some of these remaining questions for CYD-TDV can be addressed reasonably with existing data from the Phase 3 trials or future data. For example, if the existing trials collected vaccine impact on syndromic disease, this should be analyzed and reported. Post-licensure surveillance also will help to further quantify vaccine effectiveness at the population level, confirm VPDI estimates reported here, assess long-term safety, aid in determining the best timing for booster doses, and measure the indirect effect of the vaccine [18]. More generally, we suggest that VPDI and NNV should be presented alongside VE in primary trial reports and included in trial designs and analytic plans. For example, vaccines predicted to have substantial indirect effects could have a community (or cluster) rather than individually randomized design. Trials should assess both etiologically confirmed and clinically defined outcomes.

In summary, our analysis documents a reasonably high VPDI and low NNV, varying from country to country, and dependent on serotype distribution and baseline seropositivity. These findings will help public health advisory groups and policy-makers decide where and how to introduce the first dengue vaccine.

Conflict of interest statement: BDG works for Agence de Médecine Preventive (AMP), which currently receives grant specific support from GSK, Merck, Pfizer, and Sanofi Pasteur and during the past 3 years has received support from Crucell, Hilleman Laboratories, and Novartis; none of this support is or was related to dengue or dengue vaccine. BDG serves on a dengue vaccine advisory group for Sanofi Pasteur but neither he nor his organization receive remuneration for this participation. AWS reports no conflict of interest since 2011; from 2008 to 2010 she was the Principal Investigator for the adult cohort in the Phase 2 trial of the CYD-TDV vaccine in Singapore. *Funding*: No financial support was received for this study.

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